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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

004458

MAY 21 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: New "Me too" for use of IGRAN® 80 WDG (Terbutryn) for Weed Control. EPA Reg. No. 100-ALL, Acc. No. 255226, Tox. Chem. No. 125D

TO: Robert J. Taylor
Product Manager 25
Registration Division (TS-767C)

THRU: Jane Harris, Ph. D., Section Head JCH 4/1/85
Review Section 6
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: Roger Gardner, Toxicologist
Review Section 6 Roger Gardner 4-1-85
Toxicology Branch
Hazard Evaluation Division (TS-769) RGFuller 5/21/85

Actions Requested

Review of the six studies cited in the bibliography (See Appendix I below).

Recommendations and Conclusions

1. The six studies cited below are adequate to support the registration of IGRAN® 80 WDG.

2. The acute oral, inhalation, dermal, and eye irritation studies indicate that the formulation should be classified into Toxicity Category III with respect to the four types of toxicity. The skin irritation study results place the formulation into Toxicity Category IV, and the formulation was not a skin sensitizer in guinea pigs.

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APPENDIX I

Data Evaluation Records

Bibliography

Choie, D., and R. Katz. June 27, 1984. Igran® 80 WDG: Acute oral toxicity in rats. Unpublished report no. 842204 prepared by Ciba-Geigy Pharmaceuticals Research, Toxicology/ Pathology Division, Chemical Toxicology Subdivision, Safety Evaluation Facility, Summit, NJ. Submitted by Ciba-Geigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

Choie, D., and R. Katz. June 27, 1984. Igran® 80 WDG: Acute ermal toxicity in rabbits. Unpublished report no. 842178 prepared by Ciba-Geigy Pharmaceuticals Research, Toxicology/ Pathology Division, Chemical Toxicology Subdivision, Safety Evaluation Facility, Summit, NJ. Submitted by CibaGeigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

Breckenridge, C., and R. Katz. June 22, 1984. Igran® 80 WDG: Acute inhalation toxicity study in rats. Unpublished report no. 842179 prepared by Ciba-Geigy Pharmaceuticals Research, Toxicology/Pathology Division, Chemical Toxicology Subdivision, Safety Evaluation Facility, Summit, NJ. Submitted by Ciba-Geigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

Choie, D., and R. Katz. June 27, 1984. Igran® 80 WDG: Primary dermal irritation study in rabbits. Unpublished report no. 842175 prepared by Ciba-Geigy Pharmaceuticals Research, Toxicology/Pathology Division, Chemical Toxicology Subdivision, Safety Evaluation Facility, Summit, NJ. Submitted by Ciba-Geigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

Choie, D., and R. Katz. June 27, 1984. Igran® 80 WDG: Primary eye irritation study in rabbits. Unpublished report no. 842176 prepared by Ciba-Geigy Pharmaceuticals Research, Toxicology/Pathology Division, Chemical Toxicology Subdivision, Safety Evaluation Facility, Summit, NJ. Submitted by Ciba-Geigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

Choie, D., and R. Katz. June 28, 1984. Guinea pig sensitization: Igran® 80 WDG FL 840804. Unpublished report prepared by Stillmeadow, Inc., Houston, TX. Submitted by Ciba-Geigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

DATA EVALUATION RECORD

1. CHEMICAL: Terbutryn
2-tert-butylamino-4-ethylamino-6-methylthio-s-triazine

2. TEST MATERIAL: Igran® 80 WDG (76% active ingrediant, 4% related compounds)

3. STUDY/ACTION TYPE: Acute oral toxicity - rats; ("Me too" registration)

4. STUDY IDENTIFICATION: Choie, D., and R. Katz. June 27, 1984. Igran® 80 WDG: Acute oral toxicity in rats. Unpublished report no. 842204 prepared by Ciba-Geigy Pharmaceuticals Research, Toxicology/Pathology Division, Chemical Toxicology Subdivision, Safety Evaluation Facility, Summit, NJ. Submitted by Ciba-Geigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

5. REVIEWED BY:

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7. CONCLUSIONS: The results of the study indicate that Igran® 80 WDG should be classified into Toxicity Category III with respect to acute oral toxicity.

Core classification: Minimum

8. MATERIALS AND METHODS

Test species: Male and female Sprague-Dawley (Crl: COBS CD (SD) BR) rats were used. Males weighed from 200 to 234 g, and females weighed from 169 to 201 g.

Experimental procedure: Groups of 5 male and 5 female rats were given single oral doses of 500, 1000, 2000, or 4000 mg

8. MATERIALS AND METHODS (continued)

test substance per kg body weight. The test substance was suspended in water and administered by gavage. The rats were fasted overnight before treatment, and they were observed for mortality and appearance of toxicological and pharmacological signs twice daily for the 14 days that followed dosing. Surviving animals were sacrificed at the end of the observation period and necropsied. Those animals that died during the study were also necropsied. Postmortem examinations were limited to gross observations.

The LD_{50} and 95% confidence limits were calculated by probit analysis.

9. REPORTED RESULTS

Signs of toxicity noted by the authors included hypoactivity, hypotonia, salivation, and ptosis which were observed one hour after dosing. Ataxia, diarrhea, and pollakiuria were also reported to occur during the first two days following dosing. Most of the surviving animals appeared normal within three days, and none of the males given the 500 mg/kg dose exhibited toxic signs. The authors stated that all of the survivors gained weight during the 14-day observation period.

No deaths occurred in rats given the 500 mg/kg dose, while all animls receiving 4000 mg/kg and females given the 2000 mg/kg dose died. Most of the deaths were reported to occur within 5 days after treatment.

The only gross observation noted at necropsy was a dark lesion in the lung of a male rat given the 4000 mg/kg dose. No other animals were found with gross lesions according to the report.

The reported LD_{50} for both sexes was 1542 mg/kg with 95% confidence limits of 1075 to 2200 mg/kg. The LD_{50} calculated for males was 2206 with 95% confidence limits of 1202 to 7049 mg/kg. The LD_{50} was not determined for females alone because the 100% mortality in the two highest dosed groups left only two points on which to base the calculations.

None of the 5 females given the 500 mg/kg dose and 2 of the 5 given 1000 mg/kg died. The LD_{50} was estimated to be 1050 mg/kg on the basis of a graph of those two points.

10. DISCUSSION

There were adequate data to support the reported LD_{50} values.

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DATA EVALUATION RECORD

1. CHEMICAL: Terbutryn
2-tert-butylamino-4-ethylamino-6-methylthio-s-triazine

2. TEST MATERIAL: Igran® 80 WDG (76% active ingrediant, 4% related compounds)

3. STUDY/ACTION TYPE: Acute dermal toxicity - rabbits; ("Me too" registration)

4. STUDY IDENTIFICATION: Choie, D., and R. Katz. June 27, 1984. Igran® 80 WDG: Acute dermal toxicity in rabbits. Unpublished report no. 842178 prepared by Ciba-Geigy Pharmaceuticals Research, Toxicology/Pathology Division, Chemical Toxicology Subdivision, Safety Evaluation Facility, Summit, NJ. Submitted by Ciba-Geigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

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Signature: Jane Harris
Date: 4/11/85

7. CONCLUSIONS: The results of the study indicate that Igran® 80 WDG should be classified into Toxicity Category III with respect to acute dermal toxicity.

Core classification: Guideline

8. MATERIALS AND METHODS

Test species: Male and female New Zealand White strain rabbits weighing 3.1 to 3.6 kg (males) or 3.1 to 4.0 kg (females) were used

Experimental procedure: Twenty-four hours before the beginning of the study, the rabbits were prepared by clipping their backs free of hair (approximately 10% of the body surface

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8. MATERIALS AND METHODS (continued)

area). The report stated that 5 animals of each sex were used in a "limit test."

The test substance was suspended in water at a concentration of 670 mg/ml, and 3 ml/kg was applied to the prepared skin site. A total of 2010 mg/kg was applied to each rabbit.

After the application of test substance, the trunks of the test animals were wrapped with gauze which was secured with adhesive tape. These dressings were then covered with orthopedic stockinets to prevent ingestion of the test substance during the 24 hour exposure. At the end of the exposure period the dressings were removed, and the test sites were gently rinsed and wiped clean.

All animals were observed twice daily for the next 14 days for the appearance of toxic signs and mortality. The rabbits were weighed on the day of dosing and on days 7 and 14 of the observation period. Surviving rabbits were sacrificed at the end of the 14-day observation period, and gross postmortem examinations were conducted.

9. REPORTED RESULTS

The authors noted no deaths, and the only sign of compound-related effects were the flaking of the skin at test sites on two rabbits. All animals gained weight during the study.

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DATA EVALUATION RECORD

1. CHEMICAL: Terbutryn
2-tert-butylamino-4-ethylamino-6-methylthio-s-triazine

2. TEST MATERIAL: Igran® 80 WDG (76% active ingrediant, 4% related compounds)

3. STUDY/ACTION TYPE: Acute inhalation toxicity - rats; ("Me too" registration)

4. STUDY IDENTIFICATION: Breckenridge, C., and R. Katz. June 22, 1984. Igran® 80 WDG: Acute inhalation toxicity study in rats. Unpublished report no. 842179 prepared by Ciba-Geigy Pharmaceuticals Research, Toxicology/Pathology Division, Chemical Toxicology Subdivision, Safety Evaluation Facility, Summit, NJ. Submitted by Ciba-Geigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

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7. CONCLUSIONS: The results of the study indicate that Igran® 80 WDG should be classified into Toxicity Category III with respect to acute inhalation toxicity.

Core classification: Minimum

8. MATERIALS AND METHODS

Test species: Male and female Sprague-Dawley rats were used. Males weighed from 299 to 357 g, and females weighed from 210 to 244 g. The animals were 8 to 11 weeks of age.

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8. MATERIALS AND METHODS (continued)

Experimental procedure: The test atmosphere was generated by a Trost Air Mill. The test substance was discharged into a 200 liter test chamber through which the air flowed at a rate of 60 l/min. Air concentrations and particle size distributions were measured at hourly intervals, and temperature and humidity were measured at half-hour intervals during the 4-hour exposure period. The air concentration was determined gravimetrically using an open-faced filter. Particle size distribution was determined with a cascade impactor. Timing of the 4-hour exposure period was not started until 15 minutes after discharging of the test substance into the test chamber began.

Two groups of 5 male and 5 female rats were exposed to air containing an expected 0 or 2 mg/l concentration of the test substance. The rats were placed in wire mesh cages inside the test chamber, but because of the dense test atmosphere during the 4-hour exposure period, they were not observed. After exposure, the animals were observed twice a day for the appearance of toxic signs and mortalities. These observations were continued for 14 days after exposure.

All rats found dead during the study or sacrificed after 14 days were necropsied, and gross observations were noted. Special attention was given to the eyes, nasal passages, skin, bronchi, lungs, and trachea. The lungs were weighed, perfused with buffered formalin, and kept along with the liver, kidneys, and abnormally appearing tissues. No histological examinations were conducted according to the report.

9. REPORTED RESULTS

The reported temperature and humidity for the control group animals were 78° F and 57%, respectively. Those respective values for the treated group were 74° F and 45%. The stated concentrations of test substance, as determined by gravimetric methods, ranged from 2.0 to 3.5 mg/l with an average for the 4-hour exposure period of 2.5 mg/l. The nominal concentration (mass of test substance used per liters flowing through the test chamber during exposure) was reported to be 15.5 mg/l. The hourly mean mass diameter of particles ranged from 2.1 to 2.4 um with a geometric mean standard deviation ranging from 1.9 to 2.1. Particles with an equivalent aerodynamic diameter of $\leq$ 9 um accounted for approximately 97% of the total.

There were no mortalities observed during the study.

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9. REPORTED RESULTS (continued)

The authors noted that the test animals became coated with the test substance during exposure, and when removed from the chamber they exhibited chromorhiorrhea, pollakiuria, and salivation. The signs were not seen after the 7th day following exposure. Other signs reported by the investigators included alopecia, lacrimation, soft feces, hematuria, tachypnea, and unkempt appearance. All of these signs, with the exception of one case of alopecia, disappeared after the 7th day of observation. Rats which were not exposed to the test substance did not appear to be abnormal according to the report.

Group mean body weights were comparable at days 7 and 14 of the observation period, and the animals gained weight during that time. There were also no differences noted with respect to group mean lung weights.

The only necropsy findings included a reddened thymus in one control group female and a male in the treated group.

10. DISCUSSION

There were adequate data to support the conclusions of the investigators .

DATA EVALUATION RECORD

1. CHEMICAL: Terbutryn
2-tert-butylamino-4-ethylamino-6-methylthio-s-triazine

2. TEST MATERIAL: Igran® 80 WDG (76% active ingrediant, 4% related compounds)

3. STUDY/ACTION TYPE: Dermal irritation study - rabbits; ("Me too" registration)

4. STUDY IDENTIFICATION: Choie, D., and R. Katz. June 27, 1984. Igran® 80 WDG: Primary dermal irritation study in rabbits. Unpublished report no. 842175 prepared by Ciba-Geigy Pharmaceuticals Research, Toxicology/Pathology Division, Chemical Toxicology Subdivision, Safety Evaluation Facility, Summit, NJ. Submitted by Ciba-Geigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

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7. CONCLUSIONS: The results of the study indicate that Igran® 80 WDG should be classified into Toxicity Category IV with respect to dermal irritation (primary irritation score = 0.29).

Core classification: Guideline

8. MATERIALS AND METHODS

Test species: Male and female New Zealand White strain rabbits weighing 3.1 to 3.9 kg (males) or 3.3 to 3.8 kg (females) were used.

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8. MATERIALS AND METHODS (continued)

Experimental procedure: Twenty-four hours before the beginning of the study, the rabbits were prepared by clipping their backs free of hair. Three animals of each sex were used.

The test substance was moistened with water, and 500 mg amounts were spread over a 6 cm^2 area of intact skin on each rabbit. The test sites were then covered with gauze patches which were secured with nonirritating adhesive tape. The trunk of each animal was then covered with an orthopedic stockinet.

Four hours after application of the test substance the dressings were removed, and the test sites were rinsed and gently wiped clean. One-half to one hour later the test sites were scored for edema and erythema, and they were scored again 24, 48, and 72 hours after removal of the dressings.

Erythema and eschar formation as well as edema were scored on a 5-point scale (0-4) with a maximum possible score of 8 for any site. Scoring was done according to the following classifications:

Erythema and eschar		Edema	
No erythema	0	No edema	0
Slight erythema	1	Very slight edema	1
Well-defined erythema	2	Slight edema	2
Moderate to severe erythema	3	Moderate edema	3
Severe erythema to slight eschar formation	4	Severe edema	4

Mean irritation scores were calculated as follows:

$$\text{Mean Score} = \frac{\text{Sum of Erythema and Edema Scores of All Animals}}{(\text{Total No. Animals})\ (\text{Total No. Scoring Time Points})}$$

Based on the results the test substance was classified according to the following scale:

Mean score	Irritation rating
0.0 - 0.4	Practically not an irritant
0.5 - 3.0	Slight irritant
3.1 - 5.0	Moderate irritant
5.1 - 7.0	Severe irritant
7.1 - 8.0	Corrosive

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9. REPORTED RESULTS

According to the report, all the animals gained weight during the study, and no clinical signs of toxicity were observed.

Two males and two females had slight erythema at the 24-hour observation, but there was none observed at 72 hours. No other signs of irritation were observed, and the mean scores were reported to be 0, 0.67, 0.5, and 0 at 0.5 to 1, 24, 48, and 72 hours, respectively with an overall mean irritation score of 0.29.

10. DISCUSSION

The report included adequate information to support the conclusion that terbutryn is practically non-irritating.

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DATA EVALUATION RECORD

1. CHEMICAL: Terbutryn
2-tert-butylamino-4-ethylamino-6-methylthio-s-triazine

2. TEST MATERIAL: Igran® 80 WDG (76% active ingrediant, 4% related compounds)

3. STUDY/ACTION TYPE: Eye irritation study - rabbits; ("Me too" registration)

4. STUDY IDENTIFICATION: Choie, D., and R. Katz. June 27, 1984. Igran® 80 WDG: Primary eye irritation study in rabbits. Unpublished report no. 842176 prepared by Ciba-Geigy Pharmaceuticals Research, Toxicology/Pathology Division, Chemical Toxicology Subdivision, Safety Evaluation Facility, Summit, NJ. Submitted by Ciba-Geigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

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Date: 4/1/85

7. CONCLUSIONS: The results of the study indicate that Igran® 80 WDG should be classified into Toxicity Category III with respect to eye irritation.

Core classification: Guideline

8. MATERIALS AND METHODS

Test species: Male and female New Zealand White strain rabbits weighing 3.1 to 3.8 kg (males) or 3.1 to 3.6 kg (females) were used.

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8. MATERIALS AND METHODS (continued)

Experimental procedure: Nine rabbits previously examined and found without signs of eye irritation or eye defects were used in the experiment. One-tenth of a gram of the test substance was instilled into the left eye of each rabbit, and the eyelids were gently held together for one second. Thirty seconds after the instillation, the treated eyes of 3 rabbits were washed for one minute with distilled water. Washing was started 30 seconds after treatment. The eyes of the 6 remaining rabbits were washed in a similar manner 24 hours after treatment.

All eyes were examined 1, 24, 48, and 72 hours after instillation of the test substance. Examinations were also conducted 7 days after treatment. Ocular reactions were scored according to the following scales:

Corneal opacity

Degree of density

1 - scattered or diffuse area, details of iris visible
2 - easily discernible transluscent areas, details of iris slightly obscured
3 - opalescent areas, no details of iris visible, size of pupil barely discernible
4 - opaque, iris invisible

Area of cornea involved

1 - one-quarter (or less but not zero)
2 - greater than one-quarter to less than one-half
3 - greater than one-half to less than three-quarters
4 - greater than three-quarters

score = score for degree x score for extent x 5
maximum = 80

Iris

1 - folds above normal, congestion, swelling, circumcorneal injection (any one or a combination of these), iris still reacting to

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8. MATERIALS AND METHODS (continued)

light (sluggish reaction is positive)
2 - no reaction to light, hemorrhage, gross destruction (any one or all of these)

score = score for iris x 5
maximum score = 10

Conjunctivae

Redness

1 - vessels definitely injected above normal
2 - more diffuse, deeper crimson red, individual vessels not discernible
3 - diffuse beefy red

Chemosis

1 - any swelling above normal (including nictitation membrane
2 - obvious swelling with parital eversion of the lids
3 - swelling of lids about half closed
4 - swelling of lids about half to completely closed

Discharge

1 - any amount different from normal (does not include small amount in inner canthus of normal animals)
2 - discharge with moistening of the lids and hairs just adjacent to the lids
3 - discharge with moistening of the lids and considerable area around the eye

Score = sum of values for redness, chemosis, and discharge multiplied by 2. Maximum = 20

The test substance was classified according to the following categories:

I. Corrosive (irreversible destruction of occular tissue) or corneal involvement or irritation persisting for more than 21 days.

II. Corneal involvement or irritation clearing in 8-21 days.

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8. MATERIALS AND METHODS (continued)

III. Corneal involvement or irritation clearing in 7 days or less.

IV. Minimal effects clearing in less than 24 hours.

9. REPORTED RESULTS

The reported mean corneal and iris scores were 0.1 at 24 hours, and at all other examinations those scores were 0.

Mean scores for the conjunctivae were 1.1, 0.8, 0.8, 0.4, and 0.0 for redness at 1, 24, 48, and 72 hours and 7 days, respectively; respective scores for chemosis were 0.1, and 0.4 for the 1 and 24 hour observations and 0 at all other examination times.

10. DISCUSSION

The report included adequate information to support the conclusions of the investigators.

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DATA EVALUATION RECORD

1. CHEMICAL: Terbutryn
2-tert-butylamino-4-ethylamino-6-methylthio-s-triazine

2. TEST MATERIAL: Igran® 80 WDG (76% active ingrediant, 4% related compounds)

3. STUDY/ACTION TYPE: Skin sensitization - guinea pig; ("Me too" registration)

4. STUDY IDENTIFICATION: Maedgen, J. L., E. J. Sabol, R. J. Sabol, R. Mendez, and L. D. Weidner. June 28, 1984. Guinea pig sensitization: Igran® 80 WDG FL 840804. Unpublished report prepared by Stillmeadow, Inc., Houston, TX. Submitted by Ciba-Geigy Corp., Agriculture Division, Greensboro, NC. EPA Acc. No. 255226.

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Date: 4/1/85

7. CONCLUSIONS: The results of the study indicate that Igran 80 WDG should not be classified as a skin sensitizer in guinea pigs.

Core classification: Minimum

8. MATERIALS AND METHODS

Test species: Male Hartley albino guinea pigs weighing from 315 to 380 g were used.

Experimental procedure: The hair was clipped from the backs of test animals 24 hours prior to the initial and final treatments (see below). Similar preparations were made on the second through the 21st days of the study.

Two groups of 10 animals were used. The first group received

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an initial application of a 0.05% solution of dinitrochloro-

8. MATERIALS AND METHODS (continued)

benzene (DNCB) in ethanol, while the second group received an application of a 10.0% solution of the test substance in deionized water. The report noted that the 10% concentration was selected on the basis of a preliminary study and is considered to be the highest non-irritating concentration that can be used. No further discussion of the preliminary study was included in the report.

Applications were made under 5/8 by 9/8 inch gauze pads secured to prepared skin sites by a 1.5 by 2 inch piece of adhesive tape. The animals were treated on days 1, 3, 6, 8, 10, 13, 15, 17, 20, 22, and 36 of the study. Body weights of the test animals were obtained on days 0, 7, 14, 21, 28, and 35. Exposures lasted for 6 hours, and at the end of that time, the gauze pads were removed and test sites were examined and scored for reactions.

Erythema and eschar formation as well as edema were scored on a 5-point scale (0-4) with a maximum possible score of 8 for any site. Scoring was done according to the following classifications:

Erythema and eschar		Edema	
No erythema	0	No edema	0
Slight erythema	1	Very slight edema	1
Well-defined erythema	2	Slight edema	2
Moderate to severe erythema	3	Moderate edema	3
Severe erythema to slight eschar formation	4	Severe edema	4

Each test site was scored 24 hours after application of the test substance. In addition, sites were scored 48 hours after the applications which were made on days 1, 10, and 36. The authors stated that an average irritation score was obtained by adding scores for each time period and dividing by the number of observations for that time period. The authors further noted that a sensitizing reaction was indicated by an increase in positive reactions after the final dose (on day 36) in comparison to the reactions after the first dose (on day 1).

9. REPORTED RESULTS

The average irritation score after the first dose in the positive control group was reported to be 0.0, and the reported average after the last DNCB dose was 2.2. The two reported

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9. REPORTED RESULTS (continued)

average irritation scores for those animals treated with the test substance were 0.0 after the first and final treatments.

10. DISCUSSION

Adequate information was included in the report to support the conclusions of the authors.

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Chemical:	**Terbutryn (ANSI)**
PC Code:	**080813**
HED File Code	**13000 Tox Reviews**
Memo Date:	**05/21/85**
File ID:	**TX004458**
Accession Number:	**412-03-0018**

HED Records Reference Center
11/26/2002